(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 May 2003 (30.05.2003)

PCT

(10) International Publication Number
WO 03/043641 A1

(51) International Patent Classification⁷: A61K 31/663, 31/734

(21) International Application Number: PCT/TR02/00055

(22) International Filing Date: 15 October 2002 (15.10.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2001/03166 19 November 2001 (19.11.2001) TR

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/043641 A1

(54) Title: NEW PHARMACEUTICAL COMBINATIONS PREPARED WITH ALGINATES AND BIPHOSPHONATES IN ORDER TO PREVENT GASTROESOPHAGEAL REFLUX DURING USE OF ORAL BIPHOSHONATES

(57) Abstract: This invention is about a method for preparation of pharmaceutic composition which contains biphosphonate derivation in such quantity to reduce loss of calcium in the bone tissue to prevent gastroesofageal reflux which occurs during use of oral biphosphonates and anti-reflux agent in such quantity to prevent gastroesofageal reflux of this biphosphonate derivation. Alginic acid and/or its salts, preferably alginic acid or sodium alginate, are used as anti-reflux agent.

DESCRIPTION

NEW PHARMACEUTICAL COMBINATIONS PREPARED WITH ALGINATES AND BIPHOSPHONATES IN ORDER TO PREVENT GASTROESOPHAGEAL REFLUX DURING USE OF ORAL BIPHOSHONATES.

This invention is about a method for preparation of a pharmaceutical composition that contains a biphosphonate derivative in a quantity to reduce loss of calcium from the bone tissue and an anti-reflux agent in a quantity to be effective in prevention of gastroesophageal reflux of this biphosphonate derivative.

Biphosphonates are synthetic analogs of pyrophospate bonded to hydroxyappetite present in the bone tissue. They are effective in prevention and treatment of cases when the mineral content of bone reduces through inhibition of osteoclasts, which are the cells responsible for bone resorption.

Osteoporosis is a term indicating reduction in the bone mass and density related to the age and metabolic disturbances. This problem generally affects post-menopausal women and elderly men. The most common clinical cases that occur related to osteoporosis are occurrence of fractures at vertebra, bones at hip and wrist. Currently a number of therapies are used and tried for solution of this problem. Development of osteoporosis is prevented, or if it is established, treated by means of Calcium and Vitamin D supplement, physical activity, selective estrogen-receptor modulators, phytoestrogens, medical products such as calcitonin, biphosphonates such as alendronate, etidronate and risedronate.

Biphosphonates are also used in other clinical indications such as Paget's disease, heterotropic ossification, hypercalcemia developed in connection with malign diseases, bone metastases which originate from malign tumors.

Common adverse effects of biphosphonates are that they cause severe gastric and esophageal disturbances. Pharmacologic characteristics and adverse effects of biphosphonates are detailed in Physician's Desk Reference 55. edition, 2001, "Upper Gastrointestinal Toxicity of Alendronate" The American Journal of Gastroenterology

2000, "Oral Bisphosphonates: A review of clinical use in patients with bone metastases" Cancer, January 1, 2000, Volume 88, Number 1, 6-14.

Reflux esophagitis occurs with passage of gastric fluid in small quantities or food or bile acids or substances with irritant characteristic present in the gastric content and an in the regions outside the gastric mucosa into the lower part of esophagus. Such types of contents cause important implications resulting in inflammation in the esophageal mucosa.

In order to prevent occurrence of these adverse effects, it is aimed at accelarating passage of the drug with one glass of water into the stomach and it is recommended that patients should not lie and rest on bed till first food of the day for at least 30 minuts in order to prevent reflux of the drug from stomach to esophagus. Furthermore, it is recommended that the drug should not be taken before going to bed or before rising up from the bed in the morning. It is stated that these recommendations are for keeping risk of the occurrence of adverse effects related to esophagus in connection with the drug to the minimum extent.

In WO 98/25628, in order to reduce these risks, a new pharmaceutical composition has been developed with alendronate sodium and active agent called cisapride that activates gastric discharge.

Alginic acid has been discovered by E.C.C.Stanford, British pharmacist, in 1883. Alginates may be different forms such as alginic acid and sodium, potassium, magnesium, calcium, ammonium salt form of its.. Alginic acid and its salts are used for treatment and prevention of esophageal reflux. These types of use of alginates are described in WO patent 95/1168, WO patent 85/04806, WO patent 97/36599, WO patent 01/66119.

This invention relates to a pharmaceutical composition that may prove to be useful in prevention of reflux esophagitis that occur during biphosphonate treatment, gastric and/or peptic ulcerations and about pharmaceutical compositions that contains alginic acid and/or one of its salts.

Esophageal and gastric disturbances have been considered as complications related to gastroesophageal reflux that is likely to appear in the patients under biphosphonate treatment. The aim of this invention is, therefore, to prepare a pharmaceutical composition of biphosphonate in effective quantity therapeutically and alginic acid and/or alginic acid salts in effective quantity therapeutically in order to prevent gastroesophageal reflux of biphosphonates***.

Alendronate is a drug that prevents loss of calcium by inhibiting osteoclasts in the bone tissue pharmacologically. It is used for treatment of the established osteoporosis in the post-menopausal women or for prevention of osteoporosis expected to develop during this period and treatment of osteoporosis developed in connection with glucocorticoid treatment and, finally, for treatment of Paget's disease. It has been launched Merck&Co. under the name of Fosamax®. This product may causes*** esophagitis due to gastric reflux. Recommended doses are 5 mg/day, 10 mg/day and 35 mg/week, 70 mg/week. It is also used as 40mg/day over 6 months for Paget's disease.

Risedronate is a pyridinyl biphosphonate. It inhibits bone resorption generated by osteoclasts in the bone tissue and regulates bone metabolism. It was launched by Procter&Gamble under the name of Actonel®. This product may causes*** esophagitis due to gastric reflux. Recommended dose for prevention and treatment of postmenopausal osteoporosis as well as osteoporosis connected to glucocorticoid is 5 mg/day. Furthermore, dose of 30 mg/day is used for Paget's disease for 2 months.

Etidronate is an agent, primarily active in the bone tissue. It inhibits formation, growth and dissolution of hydroxyappatite crystals. It also inhibits chemisorption of amorphous precursors onto the calcium phosphate surface. It has been launched by Procetr&Gamble under the name of Didronel®. Recommended dosage for Paget's disease is 5-10 mg/kg/day for a period upto 6 months and 11-20 mg/kg/day for a period upto 3 months. In the heterotrophic ossification it is started from 1 month before total Hip replacement operation to 3 months afterwards. In these patients, the dose is 20 mg/kg/day. For patients with spinal cord trauma, it is administered 20 mg/kg/day for 2 weeks and later on it is administered by 10 mg/kg/day for 10 weeks.

Tiludronate prevents loss of calcium by inhibiting osteoclast activity in the bone tissue. It creates this effect possibly by suppressing enzymatic and transport factors that cause mineral matrix resorption. It has been launched by Sanofi Synthelabo Inc. under the name of Skelid®. Recommended dose for Paget's disease is 400 mg/day.

Alginic acid and its salts are used in various compositions for treatment and prevention of esophagual reflux. When alginic acid contacts with the gastric*** content, it causes a formation that floats over the gastric content. This foamy structure serves as a mechanical barrier preventing passage of the gastric content into the esophagus. With prevention of reflux, the destructive effects of the irritant materials of the gastric content are eliminated.

This invention encompasses a pharmaceutical composition comprising an effective amount of biphosphanate derivatives for reducing calcium loss and effective amount of alginic acid and/or its salts to prevent gastroesophageal reflux.

In accordance with this invention, the active agents of the biphosphonate group and the alginates can be prepared in double-layer tablets or conventional tablets. Furthermore, alginates or active agent may be pressed in core tablet an the other part may be pressed onto it as a separate layer. Furthermore, the alginates and drugs of the biphosphonate group are also mixed and prepared in capsules. Preferabley, pharmaceutical composition in double-layer tablet is prepared.

In the composition of double-layer tablet, alginic acid and/or its salts (sodium, potassium, magnesium, calcium, ammonium, etc.) and one of the active agents of the biphosphonate group are made into a double-layer tablet. Preparation of double-layer tablet, after alginic acid and/or its salts (sodium, potassium, magnesium, calcium, ammonium, etc.) are prepared granules by wet granulation or not prepared granules (powder), these granules or powder are mixed excipients for tablet pressing. For wet granulation, polyvinylpyrolydones (PVP), gelatin, starches(such as corn starch, potato starch), starch derivatives (such as pregelatinized starch), cellulose derivations (hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, methylcellulose, etc.) can be used as binder. Preferably, PVP, pregelatinized starch or low substitute hydroxyprypolcellulose are used. Binding concentrate may be between 1-50% of the alginate.

Preferably alginic acid and sodium alginate are used which are used between 1 mg to 2000 mg, preferabley 500 mg. In the formulation filling excipients such as microcrystalline cellulose, lactose, starches are used. Preferably, microcrystalline cellulose is used between 10% and 200% of the alginate. In the formulation, lubricants and glidants such as stearic acid, magnesium stearate, talk, aerosil are also used. Preferably, magnesium stearat and aerosil are used in the formulation.

Disintigrantes such as crosscarmellose sodium, sodium starch gluconate can be used to the formulation.

In the formulation of alginates, a carbonate source such as sodium bicarbonate, sodium carbonate, calcium carbonate can be used an thus when the alginate enters into stocmach, it may be ensured to swell immediately, forming a foamy structure.

In this composition of double-layer tablet, the other layer is composed of one of biphosphonates. The active agent of the biphosphonate derivatives used is prepared granules by wet granulation or not prepared granules (powder) and then mixed with other excipients for tablet pressing. For wet granulation, polyvinylpyrolydones (PVP), gelatin, starches(such as corn starch, potato starch), starch derivatives (such as pregelatinized starch), cellulose derivations (hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, methylcellulose, etc.) can be used as binder. Preferably, PVP, pregelatinized starch or low substitute hydroxypropylcellulose are used. Binding concentrate may be between 1-50% of the biphosphanate. In the formulation filling excipients such as microcrystalline cellulose, lactose, starches are used. Preferably, microcrystalline cellulose is used between 10% and 1000% of the biphosphonates. In the formulation, lubricants and glidants such as stearic acid, magnesium stearate, talk, aerosil are also used. Preferably, magnesium stearat are used in the formulation.

Disintigrantes having superior disintigrate characteristic such as crosscarmellose sodium, sodium starch gluconate are alse added to the formulation. Preferably, crosscharmellose sodium is used in the formulation.

After alginates and biphosphonates are pressed into double-layer tablets, on the tablet machine capable of pressing two-layer tablet. From the alginates, preferably alginic acid and sodium alginate are used in doses between 1mg and 2000mg, preferably 500mg

Another type of formulation is that after alginates and biphosphonates are mixed together they are made into tablet or capsule. In this formulation, unlike from the double-layer tablet formulation, biphosphonates and alginates are mixed. From the alginates, preferably alginic acid and sodium alginate are used in doses between 1mg and 2000mg, preferably 500mg. **They have been granular with use of the above-mentioned binders or powder and mixed with filling agents, disintigrants, lubricants and glidants and pressed in tablet or filled in capsules,

Instead of double-layer tablet machine, by attaching a special apparatus to the classic tablet machine, first one of the biphosphonates or alginates are pressed as core tablet and then other substance that have not been pressed is pressed onto it as a second layer. The formulation here is same with that one in the double-layer tablet formulation.

CLAIMS:

1- An oral pharmaceutical dosage form comprising a safe and effective amount a biphosphonate derivative in such quantity to reduce loss of calcium content of the bone tissue and an anti-reflux agent in such quantity to be effective for prevention of gastroesofageal reflux of this biphosphonate derivative.

2- A dosage form according to Claim 1 where alginic acid and/or its salts (such as sodium, potassium, magnesium, calcium, ammonium) are used as anti-reflux agent.

3- A dosage form according to Claim 2 where preferably alginic acid or sodium alginate is used as antireflux agent.

4- A dosage form according to Claim 3 where alginic acid or sodium alginate between 1mg and 2000 mg, preferably 500 mg, is used.

5- A dosage form according to Claim 1 where biphosphonates that vary between 1mg and 1000mg are used.

6- A dosage form according to Claim 5 where preferably alendronate, risedronate, etydronate, tiludronate are used as biphosponate.

7- A dosage form according to Claim 1 which is made by preparation of active agents of biphosphonate derivatives and alginates in double-layer tablet or normal tablet or made by pressing alginates or active agents in core talet and other part being pressed thereon as a separate layer or prepared in capsule by mixing alginates and biphosphonate derivatives.

8- A dosage form according to Claim 7 which is prepared preferably in double-layer tablet.

9- A dosage form according to Claim 4 which is used powder or prepared granules by wet granulation and then these powder or granules are mixed with fillin agent,lubricants and glidants for pressing tablet.

10- A dosage form according to Claim 4 and 9 where preferably wet granulation method is used.

11- A dosage form according to Claim 4 and 9 where polyvinylpyrolydones (PVP), gelatin, starches (such as corn starch, potato starch), starch derivatives (such as pregelatinized starch), cellulose derivatives (hydroxpypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, metylcelluloce, etc.) are used as binder for wet granualiton.

12- A dosage form according to Claim11 where preferably PVP, pregelatinized starch or low substitute hydroxyprpopylcellulose is used.

13- A dosage form according to Claim 11 where concentration of binders is between 1%-50 of alginate.

14- A dosage form according to Claim 5 where the active agent of biphosphonate group is made granules by wet granulation and and then mixed with filling agents, lubricants and glidants or directly mixed with filling agents, lubricants and glidants without making any graunulation to make it powder or granules ready for tablet pressing.

INTERNATIONAL SEARCH REPORT

Interna I Application No
PCT/TR 02/00055

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/663 A61K31/734

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	GROEN DE P C ET AL: "ESOPHAGITIS ASSOCIATED WITH THE USE OF ALENDRONATE" NEW ENGLAND JOURNAL OF MEDICINE, THE, MASSACHUSETTS MEDICAL SOCIETY, WALTHAM, MA, US, vol. 335, no. 14, 3 October 1996 (1996-10-03), pages 1016-1021, XP002056398 ISSN: 0028-4793 the whole document	1-14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
13 March 2003	21/03/2003

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 85 04806 A (RORER INT OVERSEAS (US)) 7 November 1985 (1985-11-07) cited in the application abstract; claim 1	1-14
Y	MACONI G ET AL: "MULTIPLE ULCERATIVE ESOPHAGITIS CAUSED BY ALENDRONATE" AMERICAN JOURNAL OF GASTROENTEROLOGY, NEW YORK, NY, US, vol. 90, no. 10, 1995, pages 1889-1890, XP002056397 ISSN: 0002-9270 the whole document	1-14
Y	WO 97 36599 A (KROTKIEWSKI MARCIN (SE)) 9 October 1997 (1997-10-09) cited in the application abstract; claim 1	1-14

INTERNATIONAL SEARCH REPORT

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Interna[illegible]al Application No
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